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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/06, C07D 471/04, 521/00, A61K 38/05, 31/395 — A1

(11) International Publication Number: WO 97/24369

(43) International Publication Date: 10 July 1997 (10.07.97)

(21) International Application Number: PCT/IB96/01353

(22) International Filing Date: 4 December 1996 (04.12.96)

(30) Priority Data:
60/009,469 28 December 1995 (28.12.95) US

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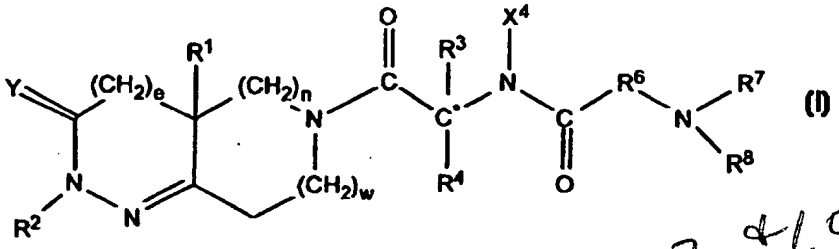
(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: GROWTH-HORMONE SECRETAGOGUES



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(57) Abstract

This invention is directed to compounds of formula (I) and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretagogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of osteoporosis, congestive heart failure, frailty associated with aging, obesity; accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating osteoporosis when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula (I).

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GROWTH-HORMONE SECRETAGOGUES

This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prev ntion of osteoporosis.

Background of the Invention

Growth hormone (GH), which is secreted from the pituitary gland, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in substantially all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

Deficiency in growth hormone results in a variety of medical disorders. In children, it causes dwarfism. In adults, the consequences of acquired GH deficiency include profound reduction in lean body mass and concomitant increase in total body fat, particularly in the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. Bone density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional benefits of therapy have included reduction in LDL cholesterol and improved psychological well-being.

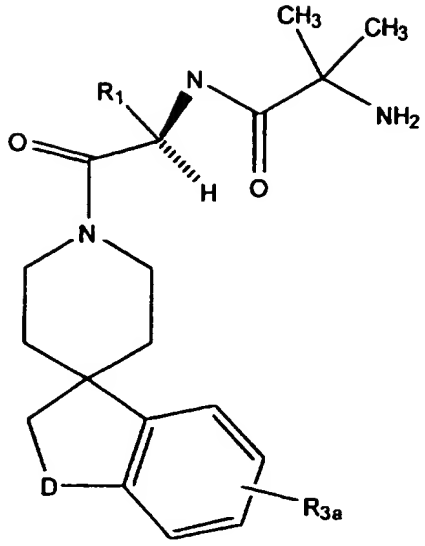
In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in an expensive product, and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone (e.g., Jacob-Creutzfeld disease). Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Most GH deficiencies are caused by defects in GH release, not primary defects in pituitary synthesis of GH. Therefore, an alternative strategy for

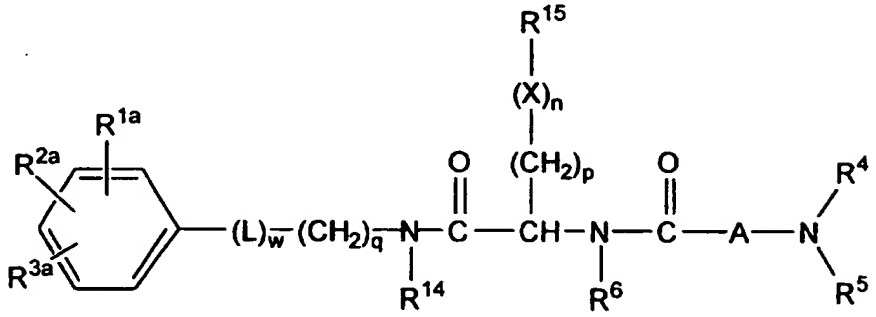
normalizing serum GH levels is by stimulating its release from somatotrophs. Increasing GH secretion can be achiev d by stimulating or inhibiting various neurotransmitter systems in the brain and hypothalamus. As a result, the development of synthetic growth hormone-releasing agents to stimulate pituitary GH secretion are being pursued, and may have several advantages over expensive and inconvenient GH replacement therapy. By acting along physiologic regulatory pathways, the most desirable agents would stimulate pulsatile GH secretion, and excessive levels of GH that have been associated with the undesirable side effects of exogenous GH administration would be avoided by virtue of intact negative feedback loops.

Physiologic and pharmacologic stimulators of GH secretion include arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GHRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

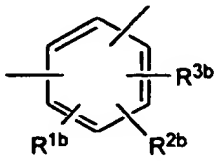
Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. WO 94/13696 refers to certain spiropiperidines and homologues which promote release of growth hormone. Preferred compounds are of the general structure shown below.



WO 94/11012 refers to certain dipeptides that promote release of growth hormone. These dipeptides have the general structure



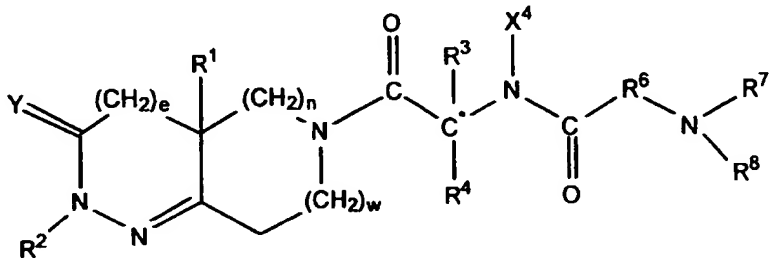
where L is



The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of osteoporosis in combination with parathyroid hormone or a bisphosphonate.

Summary of the Invention

This invention provides compounds of the formula:



(I)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1; where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

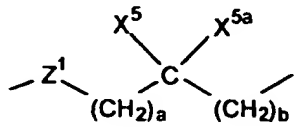
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 or $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1$-$C_6)$alkyl;

the optionally substituted $(C_1$-$C_6)$alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^2$, $(C_3$-$C_7)$cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

R^7 and R^8 are independently hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

where the optionally substituted $(C_1$-$C_6)$alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O$-$(C_1$-$C_6)$alkyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O$-$C(O)(C_1$-$C_{10})$alkyl or 1 to 3 $(C_1$-$C_6)$alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r$-L-$(CH_2)_r$-;

wh re L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for ach occurr nce is independently (C_5-C_7)cycloalkenyl, ph nyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_8)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where th optionally substitut d (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with -$S(O)_m$(C_1-C_6)alkyl, -$C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, -$S(O)_m$(C_1-C_6)alkyl, carboxylate (C_1-C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

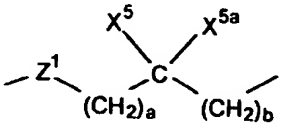
m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition -$(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

A preferred group of compounds, designated the "A Group", contains those compounds having the formula I as shown hereinabove wherein X^4 is hydrogen; R^4 is hydrogen or methyl; R^7 is hydrogen or (C_1-C_3)alkyl; R^8 is hydrogen or (C_1-C_3)alkyl optionally substituted with one or two hydroxyl groups;

R^6 is  where Z^1 is a bond and a is 0 or 1;

X^5 and X^{5a} are each independently hydrogen, trifluoromethyl, phenyl, optionally substituted (C_1-C_6)alkyl;

wher th optionally substituted (C_1-C_6)alkyl is optionally substituted with OX^2, imidazolyl, phenyl, indolyl, p-hydroxyphenyl, (C_5-C_7)cycloalkyl, -$S(O)_m$(C_1-C_6)alkyl, -$N(X^2)(X^2)$ or -$C(O)N(X^2)(X^2)$;

or X^5 and R^7 are taken together to form a (C_1-C_5)alkylene bridge, and the other substituents not defined for the "A Group" compounds are as defined for formula (I) hereinabove.

A group of compounds, which is preferred among the "A Group" of compounds, designated the "B Group", contains those compounds of the "A Group", having the formula I as shown hereinabove, wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C_1-C_3)alkyl or hydroxy(C_1-C_3)alkyl; R^3 is selected from the group consisting of 1-indolyl-CH_2-, 2-indolyl-CH_2-, 3-indolyl-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, 1-benzimidazolyl-CH_2-, 2-benzimidazolyl-CH_2-, phenyl-(C_1-C_4)alkyl-, 2-pyridyl-(C_1-C_4)alkyl-, 3-pyridyl-(C_1-C_4)alkyl-, 4-pyridyl-(C_1-C_4)alkyl-, phenyl-CH_2-S-CH_2-, thienyl-(C_1-C_4)alkyl-, phenyl-(C_0-C_3)alkyl-O-CH_2-, phenyl-CH_2-O-phenyl-CH_2-, and 3-benzothienyl-CH_2-;

where the aryl portion(s) of the groups defined for R^3 are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds, which is preferred among the "B Group" of compounds, designated the "C Group", contain those compounds of the "B Group", having the formula I as shown hereinabove, wherein R^4 is hydrogen; a is 0; n is 1 or 2; w is 0 or 1; X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen;

R^7 and R^8 are each hydrogen; and

R^3 is phenyl-CH_2-O-CH_2-, phenyl-CH_2-S-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-;

where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH_3, OCF_2H, OCF_3 and CF_3.

A group of compounds, which is preferred among th "C Group" of compounds, designated the "D Group", contains those compounds of th "C Group", having the formula I as shown hereinabove, wherein R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

where A^1 in the definition of R^1 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y is O; R^2 is hydrogen, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, phenyl or (C_1-C_8)alkyl where the (C_1-C_8)alkyl group is optionally substituted with hydroxyl, $-CF_3$ or 1 to 3 halogen.

A group of compounds, which is preferred among the "D Group" of compounds, designated the "E Group", contains those compounds of the "D Group" wherein w is 0 and n is 1.

Another group of compounds, which is preferred among the "D Group" of compounds, designated the "F Group", are those compounds of the "D Group", having the formula I as shown hereinabove, wherein e is 0; n and w are each 1;

R^1 is $-(CH_2)_t-A^1$;

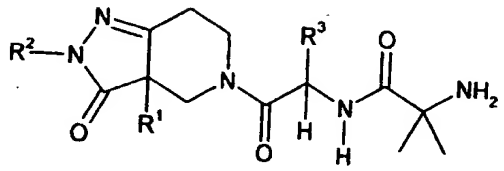
where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

t is 0, 1 or 2;

and R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 or OCF_2H.

A group of compounds, which is preferred among the "F Group" of compounds, designated the "G Group", contains those compounds of the "F Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^1 is $-CH_2$-phenyl, $-CH_2$-4-fluoro-phenyl, $-CH_2$-pyridyl or $-CH_2$-thiazolyl and R^2 is hydrogen, methyl, ethyl, t-butyl or $-CH_2CF_3$.

A group of compounds, which is pref rred among the "G Group" of compounds, designated th "G^1 Group", contains those compounds of the "G Group", and have the formula



the racemic-diastereomeric mixtures and optical isomers of said compounds wherein

R^1 is -CH_2-phenyl, R^2 is methyl and R^3 is -$(CH_2)_3$-phenyl;

R^1 is -CH_2-phenyl, R^2 is methyl and R^3 is 3-indolyl-CH_2-;

R^1 is -CH_2-phenyl, R^2 is ethyl and R^3 is 3-indolyl-CH_2-;

R^1 is -CH_2-4-fluoro-phenyl, R^2 is methyl and R^3 is 3-indolyl-CH_2-;

R^1 is -CH_2-phenyl, R^2 is methyl and R^3 is -CH_2-O-CH_2-phenyl;

R^1 is -CH_2-phenyl, R^2 is ethyl and R^3 is -CH_2-O-CH_2-phenyl;

R^1 is -CH_2-phenyl, R^2 is -CH_2-CF_3 and R^3 is -CH_2-O-CH_2-phenyl;

R^1 is -CH_2-4-fluoro-phenyl, R^2 is methyl and R^3 is -CH_2-O-CH_2-phenyl;

R^1 is -CH_2-phenyl, R^2 is t-butyl and R^3 is -CH_2-O-CH_2-phenyl; or

R^1 is -CH_2-phenyl, R^2 is methyl and R^3 is -CH_2-O-CH_2-3,4-di-fluoro-phenyl.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(3,4-difluoro-benzyl-oxymethyl)-2-oxo-ethyl]-2-methyl-propionamide is preferred among the "G^1 Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds, which is preferred among the "G Group" of compounds, designated the "H Group", contains those compounds of the "G Group", having the formula I as shown hereinabove, wherein R^1 is -CH_2-phenyl and R^3 is phenyl-$(CH_2)_3$-.

The diastereomeric mixture of 2-amino-N-[1-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide is preferred among the "H Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds, which is preferred among the "G Group" of compounds, designat d the "I Group", contains those compounds of the "G Group" wherein R^1 is -CH_2-phenyl or -CH_2-4-fluoro-phenyl and R^3 is 3-indolyl-CH_2-.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is also preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is also preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds which is preferred among the "G Group" of compounds, designated the "J Group", contains those compounds of the "G Group" wherein R^1 is -CH_2-phenyl or -CH_2-4-fluoro-phenyl and R^3 is phenyl-CH_2-O-CH_2-.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is preferred among the "J Group" of compounds, the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture, the 3a-(R) isomer is preferred over the 3a-(S) isomer, and the L-tartaric acid salt of the 3a-(R) isomer is a preferred salt.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-{2-[3a-(R,S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-isobutyramide is also preferred among the "J Group"

of compounds, the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture and the 3a-(R) isomer is preferred over the 3a-(S) isomer.

The diastereomeric mixture of 2-amino-N-[1-(R)-benzyloxymethyl-2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a;4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds which is preferred among the "D Group" of compounds, designated the "K Group", contains those compounds of the "D Group" wherein e is 1; n is 1; w is 1; R^1 is $-(CH_2)_t-A^1$;

where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

t is 0, 1 or 2;

and R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 or OCF_2H.

A group of compounds which is preferred among the "K Group" of compounds, designated the "L Group", are those compounds of the "K Group" wherein X^5 and X^{5a} are each methyl; R^1 is -CH_2-phenyl, -CH_2-4-fluoro-phenyl, -CH_2-pyridyl or -CH_2-thiazolyl and R^2 is hydrogen, methyl, ethyl, t-butyl or -CH_2CF_3.

A group of compounds which is preferred among the "L Group", designated the "L^1 Group", are those compounds of the "L Group" wherein R^1 is -CH_2-phenyl; R^2 is hydrogen or methyl and R^3 is -CH_2-O-CH_2-phenyl.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is preferred among the "J Group", the separated 3a-(R) and 3a-

(S) isomers are preferred of th diastereomeric mixture and the 3a-(R) isomer is pref rred over the 3a-(S) isomer.

Another group of compounds, which is preferred among the "A Group" of compounds, designated the "M Group", contains those compounds of the "A Group", having the formula I as shown hereinabove, wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C_1-C_3)alkyl or hydroxy(C_1-C_3)alkyl;

R^3 is selected from the group consisting of 1-indolyl-CH_2-, 2-indolyl-CH_2-, 3-indolyl-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, 1-benzimidazolyl-CH_2-, 2-benzimidazolyl-CH_2-, phenyl-(C_1-C_4)alkyl-, 2-pyridyl-(C_1-C_4)alkyl-, 3-pyridyl-(C_1-C_4)alkyl-, 4-pyridyl-(C_1-C_4)alkyl-, phenyl-CH_2-S-CH_2-, thienyl-(C_1-C_4)alkyl-, phenyl-(C_0-C_3)alkyl-O-CH_2-, phenyl-CH_2-O-phenyl-CH_2-, 3-benzothienyl-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2-, pyrimidyl-CH_2-O-CH_2- and phenyl-O-CH_2-CH_2;

where the aryl portion(s) of the groups defined for R^3 are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

A group of compounds, which is preferred among the "M Group" of compounds, designated the "M^1 Group", contains those compounds of the "M Group", having the formula I as shown hereinabove, wherein R^4 is hydrogen; a is 0; n is 1; w is 1; e is 0; X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen; R^7 and R^8 are each hydrogen; Y is oxygen; R^2 is hydrogen, methyl, ethyl, propyl, i-propyl, t-butyl, -CH_2CF_3, CF_3 or -CH_2-cyclopropyl; R^1 is CH_2-A^1; where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; and R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$-, 3-indolyl-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2- , pyridyl-CH_2-O-CH_2- , pyrimidyl-CH_2-O-CH_2- or phenyl-O-CH_2-CH_2, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

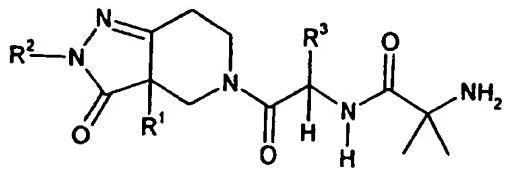
A group of compounds, which is preferred among the "M^1 Group" of compounds, designated the "N Group", contains thos compounds of the "M^1

Group", having the formula I as shown hereinabove, wh rein X^5 and X^{5a} are ach methyl; R^2 is m thyl, thyl, or $-CH_2CF_3$; A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or thienyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

Another group of compounds, which is preferred among the "M^1 Group" of compounds, designated the "O Group", contains those compounds of the "M^1 Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3; A^1 is 2-pyridyl or 3-pyridyl optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or thienyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

Another group of compounds, which is preferred among the "M^1 Group" of compounds, designated the "P Group", contains those compounds of the "M^1 Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3; A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; R^3 is 2-pyridyl-CH_2-O-CH_2-, or 3-pyridyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

A group of compounds, which is preferred among the "O Group" of compounds, designated the "Q Group", contains those compounds of the "O Group", having the formula



th racemic-diastereomeric mixtures and optical isom rs of said compounds wh rein R^2 is methyl; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-3-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-4-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-2,4-di-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-3-chloro-thiophene; or

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-2,4-di-fluoro-phenyl.

The diastereomeric mixture of 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-{1-(R)-(3-chloro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

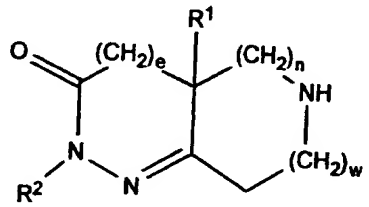
The diastereomeric mixture of 2-amino-N-{1-(R)-(4-chloro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

Th diastereom ric mixture of 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds which contains intermediates useful in synthesizing the compounds of formula (I) are of the formula



(II)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts thereof, wherein e is 0 or 1; n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 to 3 fluoro; Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-; q is 0, 1, 2, 3 or 4; t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with 1 to 3 fluoro, 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$,

$-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, or 1H-tetrazol-5-yl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1; where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted by hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted by one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally

substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, or optionally substituted $(C_3$-$C_7)$cycloalkyl, where the optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^3 for each occurrence is independently hydrogen or $(C_1$-$C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, $(C_3$-$C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted by, hydroxyl, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1$-$C_6)$alkyl, $-CO_2(C_1$-$C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 $(C_1$-$C_4)$alkyl; or

where there are two X^6 groups on one atom and both X^6 are $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^2 is hydrogen then R^1 is not -CH=CH-phenyl.

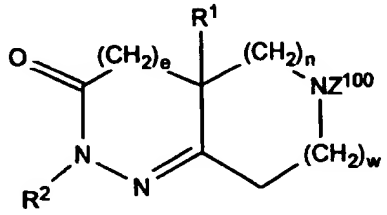
A group of intermediate compounds preferred among the foregoing group of formula (II), designated "Group AA", contains those compounds wherein w is 0 or 1; n is 1; R^1 is hydrogen, $-(CH_2)_q-(C_3$-$C_7)$cycloalkyl, $-(CH_2)_t-A^1$ or $(C_1$-$C_{10})$alkyl where the $(C_1$-$C_{10})$alkyl and $(C_3$-$C_7)$cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, methoxy, CF_3, OCF_3

and OCF_2H; R^2 is hydrog n, (C_1-C_8)alkyl, (C_0-C_3)alkyl-(C_3-C_7)cycloalkyl, phenyl, or (C_1-C_3)alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3, OH and methoxy.

A group of compounds preferred among the "AA Group" compounds, designated "BB Group", contains those compounds of "AA Group" wherein w is 1; e is 0; R^1 is $-CH_2$-pyridyl, $-CH_2$-thiazolyl, or $-CH_2$-phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, (C_1-C_4)alkyl or phenyl where the (C_1-C_4)alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

Compounds which are preferred among the "BB Group" compounds is the diastereomeric mixture of a compound wherein R^1 is $-CH_2$-phenyl and R^2 is methyl or hydrogen; and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

Another group of intermediate compounds which are useful in the synthesis of the compounds of formula (I) have the formula



(III)

the racemic-diastereomeric mixtures and optical isomers of said compounds wherein Z^{100} is methyl, BOC, CBZ, $CF_3C(O)$-, FMOC, TROC, trityl, tosyl, $CH_3C(O)$- or optionally substituted benzyl which optionally substituted with methoxy, dimethoxy or nitro; e is 0 or 1; n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,

$-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$, -C(O)O, $-OC(O)N(X^6)$ or -OC(O);

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl,

$-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, haloph nyl, methyl n di xy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 (C_1-C_4)alkyl; or

where there are two X^6 groups on one atom and both X^6 are (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the

two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12};

when R^2 is hydrogen then R^1 is not -CH=CH-phenyl;

when R^2 is H and R^1 is $-CH_2$-CH=CH-Ph, then Z^{100} is not BOC;

when R^2 is H and R^1 is then Z^{100} is not BOC;

when R^2 is H and R^1 is $-CH_2-C(CH_3)=CH_2$, then Z^{100} is not BOC; and

when R^2 is phenyl and R^1 is $-CH_3$, then Z^{100} is not $CH_3C(O)$-.

A group of compounds preferred among the foregoing group of compounds of formula (III), designated "CC Group", are those compounds wherein w is 0 or 1; n is 1;

Z^{100} is BOC, methyl, benzyl or CBZ;

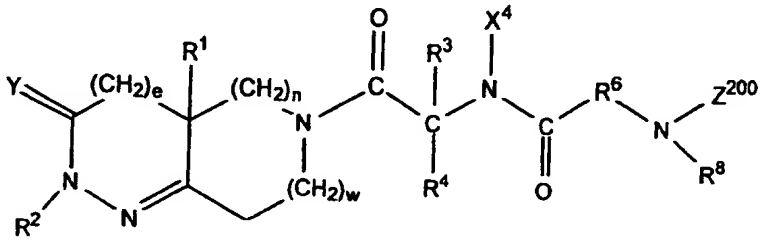
R^1 is hydrogen, $-(CH_2)_q-(C_3$-$C_7)$cycloalkyl, $-(CH_2)_t-A^1$ or $(C_1$-$C_{10})$alkyl where the $(C_1$-$C_{10})$alkyl and $(C_3$-$C_7)$cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

R^2 is hydrogen, $(C_1$-$C_8)$alkyl, $-(C_0$-$C_3)$alkyl-$(C_3$-$C_7)$cycloalkyl, phenyl, or $-(C_1$-$C_3)$alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3, OH and OMe.

A group of compounds preferred among the "CC Group" compounds, designated "DD Group", contains those compounds of "CC Group" wherein Z^{100} is BOC; w is 1; e is 0; R^1 is $-CH_2$-pyridyl, $-CH_2$-thiazolyl, or $-CH_2$-phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, $(C_1$-$C_4)$alkyl or phenyl where the $(C_1$-$C_4)$alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy and methoxy.

Compounds which are preferred among the "DD Group" compounds is the diastereomeric mixture of a compound wherein R^1 is -CH_2-phenyl and R^2 is methyl or hydrogen; and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

Yet another group of compounds which are useful in the synthesis of the compounds of formula (I) contains those compounds of the formula



(IV)

the racemic-diastereomeric mixtures and optical isomers of said compounds wherein Z^{200} is t-BOC, CBZ, $CF_3C(O)$-, FMOC, TROC, trityl, tosyl or optionally substituted benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^5$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$, $-C(O)O$, $-OC(O)N(X^6)$ or $-OC(O)$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1; where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

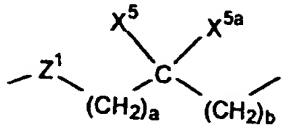
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 or $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 is optionally substituted with $-S(O)_m(C_1-C_8)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_8)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_8)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is 

;

wh re a and b are independ ntly 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, $-OX^2$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^2$, (C_3-C_7)cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 and X^{5a} forms an alkylene bridge with the nitrogen atom bearing Z^{200} and R^8 where the alkylene bridge contains 1 to 5 carbon atoms provided that X^5 or X^{5a} but not both may be on the carbon atom and Z^{200} or R^8 but not both may be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^8 is hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1-C_6)$alkyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$alkyl or 1 to 3 (C_1-C_6)alkoxy; or

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 het roatoms independently selected from th group consisting of

oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^5)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are

optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 $-OX^3$;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 (C_1-C_4)alkyl; or

when there are two X^6 groups on one atom and both X^6 are (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted by hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is 2 or 3.

Compounds which are preferred of the foregoing compounds of formula (IV) is the compound wherein e is 0; Y is O; R^1 is $-CH_2$-phenyl; R^2 is methyl or hydrogen; n is 1; w is 1; R^3 is $-CH_2-O-CH_2$-phenyl; R^4 is hydrogen; X^4 is hydrogen; R^6 is $-C(CH_3)_2-$; Z^{200} is BOC and R^8 is hydrogen.

This invention also provides:

a method for increasing levels of endogenous growth hormone in a human or other animal which comprises administering to such human or other animal an effective amount of a compound of Formula I;

a pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an inert carrier and an effective amount of a compound of Formula I;

a pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which

compris s an inert carrier, an effective amount of a compound of Formula I and anoth r growth hormone secretagogue such as, GHRP-6, Hexarelin, GHRP-1, IGF-1, IGF-2, B-HT920 or growth hormone releasing factor (GRF) or an analog thereof;

a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing osteoporosis;

a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of a bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound of Formula I;

a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of estrogen or Premarin® and a compound of Formula I and optionally progesterone;

a method to increase IGF-1 levels in IGF-1 deficient humans or other animals which comprises administering to a human or other animal with IGF-1 deficiency a compound of Formula I;

a method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula I;

a particularly preferred method for the treatment of osteoporosis comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or antagonist such as *Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyph nyl)-5-[4-(2-pip ridin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-isoquinoline and a compound of Formula I;

a method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of calcitonin and a compound of Formula I;

a method for increasing muscle mass, which method comprises administering to a human or other animal in need of such treatment an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone; and

a method for promoting growth in growth hormone deficient children which comprises administering to a growth hormone deficient child a compound of Formula I which is effective in promoting release of endogenous growth hormone.

This invention further provides a method for treating or preventing diseases or conditions which may be treated or prevented by growth hormone which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone.

In another aspect, this invention provides methods for treating or preventing congestive heart failure, frailty associated with aging, and obesity which comprise administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone; of the instant method it is preferred that the disease or condition to be treated or prevented is congestive heart failure or frailty associated with aging.

In another aspect, this invention provides methods for accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as AIDS and cancer, accelerating wound healing, and accelerating the recovery of burn patients or patients having undergone major surgery, which comprise administering to a human or other animal in need of such treatment an amount of a compound of Formula I which is effective in promoting releas of endogenous growth hormone; of the instant

method a preferred method of use is to accelerat bone fracture repair or for accelerating the recov ry of patients having undergone major surgery.

In yet another aspect, this invention provides methods for improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis and renal homeostasis, which comprise administering to a human or other animal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

The instant compounds promote the release of growth hormone which are stable under various physiological conditions and may be administered parenterally, nasally or by the oral route.

Detailed Description of the Invention

One of ordinary skill will recognize that certain substituents listed in this invention may have reduced chemical stability when combined with one another or with heteroatoms in the compounds. Such compounds with reduced chemical stability are not preferred.

In general the compounds of Formula I can be made by processes which include processes known in the chemical arts for the production of compounds. Certain processes for the manufacture of Formula I compounds are provided as further features of the invention and are illustrated by the following reaction schemes.

In the above structural formulae and throughout the instant application, the following terms have the indicated meanings unless expressly stated otherwise:

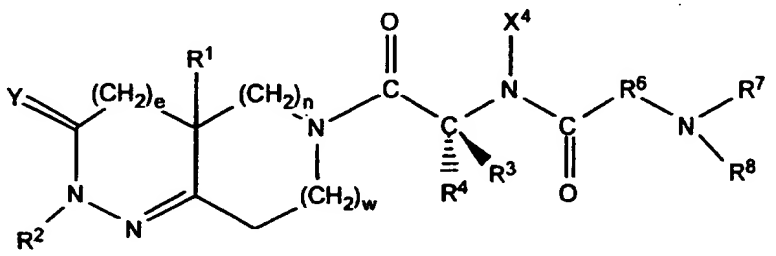
The alkyl groups are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, ethynyl, propenyl, butadienyl, hexenyl and the like.

When the definition C_0-alkyl occurs in the definition, it means a single covalent bond.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy,

TRH	Thyrotropin rel asing hormone
TROC	2,2,2-Trichloroethoxycarbonyl

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I, above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the scope of the instant invention. In the case of the asymmetric center represented by the asterisk, it has been found that the absolute stereochemistry of the more active and thus more preferred isomer is shown in Formula IA. This preferred absolute configuration also applies to Formula I.



(IA)

With the R^4 substituent as hydrogen, the spatial configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also designated an R-configuration although this will vary according to the values of R^3 and R^4 used in making R- or S-stereochemical assignments.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, D-tartaric, L-tartaric, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counter-ion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The pharmaceutically acceptable salts are formed by taking about 1 equivalent of a compound of formula (I) and contacting it with about 1 equivalent of

the appropriate corresponding acid of the salt which is desired. Work-up and isolation of the resulting salt is well-known to those of ordinary skill in the art.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release.

The compounds of Formula I can be administered to animals, including humans, to release growth hormone *in vivo*. The compounds are useful for treatment of symptoms related to GH deficiency; stimulate growth or enhance feed efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of bone or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion will alter body composition and modify other GH-dependent metabolic, immunologic or developmental processes. For example, the compounds of the present invention can be given to chickens, turkeys, livestock animals (such as sheep, pigs, horses, cattle, etc.), companion animals (e.g., dogs) or may have utility in aquaculture to accelerate growth and improve the protein/fat ratio. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier. Optionally, the pharmaceutical compositions can further comprise an anabolic agent in addition to at least one of the compounds of Formula I or another compound which exhibits a

different activity, e.g., an antibiotic growth permittant or an ag nt to treat osteoporosis or with other pharmaceutically activ materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, PTH, diethylstilbesterol, estrogens, ß-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, the disclosure of which is hereby incorporated by reference, e.g., zeranol; compounds disclosed in U.S. Patent No. 4,036,979, the disclosure of which is hereby incorporated by reference, e.g., sulbenox; and peptides disclosed in U.S. Patent No. 4,411,890, the disclosure of which is hereby incorporated by reference.

The growth hormone secretagogues of this invention in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6 and GHRP-1 as described in U.S. Patent No. 4,411,890, the disclosure of which is hereby incorporated by reference, and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or µ-adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine, are useful for increasing the endogenous levels of GH in mammals. The combination of a GH secretagogue of this invention with GRF results in synergistic increases of endogenous growth hormone.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous [See "Human Growth Hormone", Strobel and Thomas, **Pharmacological Reviews**, 46, pg. 1-34 (1994); T. Rosen et al., **Horm Res**, 1995; 43: pp. 93-99; M. Degerblad et al., **European Journal of Endocrinology**, 1995, 133: pp.180-188; J. O. Jorgensen, **European Journal of Endocrinology**, 1994, 130: pp. 224-228; K. C. Copeland et al., **Journal of Clinical Endocrinology and Metabolism**, Vol. 78 No. 5, pp. 1040-1047; J. A. Aloi et al., **Journal of Clinical Endocrinology and Metabolism**, Vol. 79 No. 4, pp. 943-949; F. Cordido et al., **Metab. Clin. Exp.**, (1995), 44(6), pp. 745-748; K. M. Fairhall et al., **J. Endocrin l.**, (1995), 145(3), pp. 417-426; RM. Fri boes et al.,

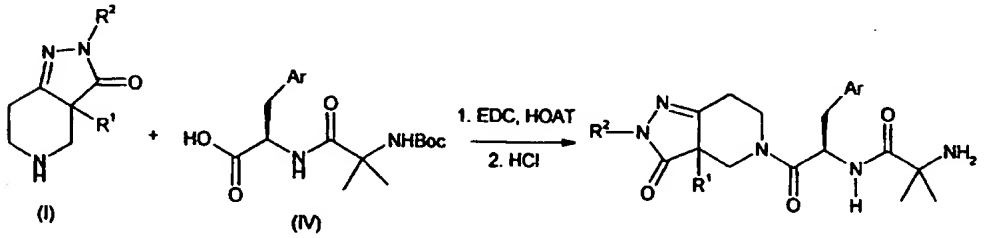
Neur end crin logy, (1995), 61(5), pp. 584-589; and M. Llovera et al., **Int. J. Canc r**, (1995), 61(1), pp. 138-141]. Thus, the administration of th compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating osteoporosis, stimulating the immune system, acceleration of wound healing, accelerating bone fracture repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/28173 and WO 95/28174 (an example of a method for assaying growth hormone secretagogues for efficacy in treating congestive heart failure is disclosed in R. Yang et al., **Circulation**, Vol. 92, No. 2, p.262, 1995), treating acute or chronic renal failure or insufficiency, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treating obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating osteochondrodysplasias, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating protein catabolic response after a major operation; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treating hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulating thymic development and preventing age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treating immunosuppressed patients and enhancing antibody response following vaccination; improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating osteoblasts, bone remodelling, and cartilage growth; treating neurological diseases such as peripheral

164	d1	Me	4-Ph-Ph	591	APCI
165	d1,2	Et	2,4-di-Cl-Ph	597	APCI
166	d1,2	Et	2,4-F-Ph	566	APCI
167	d1	Et	4-CF_3-Ph	598	APCI
168	d1,2	Et	4-CF_3-Ph	598	APCI
169	d1	Et	4-Cl-Ph	563	PB
170	d2	Et	4-Cl-Ph	563	PB
171	d1,2	Et	4-F-Ph	547	APCI
172	d1,2	Et	4-Me-Ph	543	APCI
173	d1,2	CF_3CH_2	2,4-di-Cl-Ph	651.5	APCI
174	d1,2	CF_3CH_2	2,4-di-F-Ph	620	APCI
175	d1	CF_3CH_2	4-Cl-Ph	617	PB
176	d2	CF_3CH_2	4-Cl-Ph	617	PB
177	d1	CF_3CH_2	4-F-Ph	601	APCI
178	d2	CF_3CH_2	4-F-Ph	601	APCI
179	d1,2	CF_3CH_2	4-Me-Ph	597	APCI

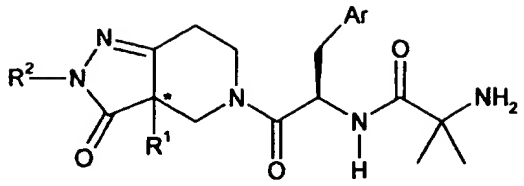
Note: in the above table, the isomer designation refers to the stereochemistry at the C-3 position (indicated by the "*" in the structure) of the pyrazalone-piperidine group; d1 and d2 refer to isomers that were chromatographically separated; d1,2 refers to a mixture of isomers.

Examples 180 - 183

Examples 180 to 183 shown in the table below were prepared according to the scheme illustrated below by coupling the appropriately substituted pyrazalone-piperidine I with the acid intermediate IV in an analogous manner to the procedures described in Examples 3E and 3F.



The acid intermediate (IV) was prepared by treating an amino acid with the product from Example 5D using the established procedure described in Example 5F.

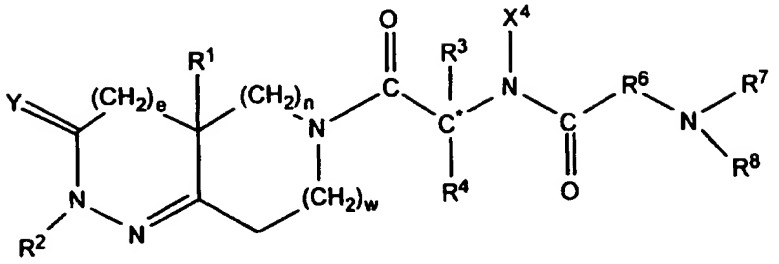


Ex. #	Isomer	R^2	R^1= -CH_2-A^1	Ar	MS	Method
180	d1,2	Me	Phenyl	$(CH_2)_2Ph$	504	PB
181	d1,2	Me	Phenyl	SCH_2Ph	559	PB
182	d1	Me	Phenyl	2-Naphthalenyl	527	APCI
183	d1,2	Me	Phenyl	CH_2O-(4-F-Ph)	524	PB

Note: in the above table, the isomer designation refers to the stereochemistry at the C-3 position (indicated by the "*" in the structure) of the pyrazalone-piperidine group; d1 and d2 refer to isomers that were chromatographically separated; d1,2 refers to a mixture of isomers.

CLAIMS

1. A compound of the formula



(I)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts and prodrugs thereof,

wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, -CH=CH-, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$, $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each b optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1, 2 or 3 halogen;

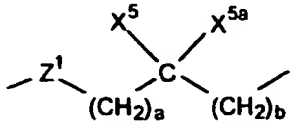
R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 or $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6)alkyl or (C_3-C_7)cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7)cycloalkyl, (C_5-C_7)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6)alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6)alkyl;

th optionally substituted (C_1-C_6)alkyl in the definition of X^5 and X^{5a} is optionally substitut d with a substituent selected from the group consisting of A^1, OX^2, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^2$, (C_3-C_7)cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1, $-C(O)O-(C_1-C_6)$alkyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$alkyl or 1 to 3 (C_1-C_6)alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently (C_5-C_7)cycloalkyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for ach occurrenc is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with -$S(O)_m$(C_1-C_6)alkyl, -$C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, -$S(O)_m$(C_1-C_6)alkyl, carboxylate (C_1-C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition -$(CH_2)_r$-L-$(CH_2)_r$- is independently 2 or 3.

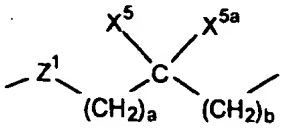
2. A compound according to claim 1 wherein

X^4 is hydrogen;

R^4 is hydrogen or methyl;

R^7 is hydrogen or (C_1-C_3)alkyl;

R^8 is hydrogen or (C_1-C_3)alkyl optionally substituted with one or two hydroxyl groups;

R^6 is  where Z^1 is a bond and a is 0 or 1;

X^5 and X^{5a} are each independently hydrogen, trifluoromethyl, phenyl, or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl is optionally substituted with OX^2, imidazolyl, phenyl, indolyl, p-hydroxyphenyl, (C_5-C_7)cycloalkyl, $-S(O)_m(C_1-C_6)$alkyl, $-N(X^2)(X^2)$ or $-C(O)N(X^2)(X^2)$;

or X^5 and R^7 are taken together to form a (C_1-C_5)alkylene bridge.

3. A compound according to claim 2 wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C_1-C_3)alkyl or hydroxy(C_1-C_3)alkyl;

R^3 is selected from the group consisting of 1-indolyl-CH_2-, 2-indolyl-CH_2-, 3-indolyl-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, 1-benzimidazolyl-CH_2-, 2-benzimidazolyl-CH_2-, phenyl-(C_1-C_4)alkyl-, 2-pyridyl-(C_1-C_4)alkyl-, 3-pyridyl-(C_1-C_4)alkyl-, 4-pyridyl-(C_1-C_4)alkyl-, phenyl-CH_2-S-CH_2-, thienyl-(C_1-C_4)alkyl-, phenyl-(C_0-C_3)alkyl-O-CH_2-, phenyl-CH_2-O-phenyl-CH_2- and 3-benzothienyl-CH_2-;

where the aryl portion(s) of the groups defined for R^3 are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

4. A compound according to claim 3 wherein

R^4 is hydrogen;

a is 0;

n is 1 or 2;

w is 0 or 1;

X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen;

R^7 and R^8 are each hydrogen; and

R^3 is phenyl-CH_2-O-CH_2-, phenyl-CH_2-S-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-;

where the aryl portion of the groups defined for R^3 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH_3, OCF_2H, OCF_3 and CF_3.

5. A compound according to claim 4 wherein

R^1 is $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl or (C_1-C_{10})alkyl;

wh r A^1 in the definition of R^1 is optionally substituted with one to three substituents, each substituent being independently s lected from the group consisting of fluoro, chloro, methyl, OCH_3, OCF_2H, OCF_3 and CF_3;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y is O;

R^2 is hydrogen, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, phenyl or (C_1-C_8)alkyl where the (C_1-C_8)alkyl group is optionally substituted with hydroxyl, $-CF_3$ or 1 to 3 halogen.

6. A compound according to claim 5 wherein w is 0 and n is 1.

7. A compound according to claim 5 wherein e is 0; n and w are each 1;

R^1 is $-(CH_2)_t-A^1$;

where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

t is 0, 1 or 2;

and R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

8. A compound according to claim 7 wherein X^5 and X^{5a} are each methyl; R^1 is $-CH_2$-phenyl, $-CH_2$-4-fluoro-phenyl, $-CH_2$-pyridyl or $-CH_2$-thiazolyl and R^2 is hydrogen, methyl, ethyl, t-butyl or $-CH_2CF_3$.

9. A compound according to claim 8 wherein R^1 is $-CH_2$-phenyl and R^3 is phenyl-$(CH_2)_3$-.

10. The diastereomeric mixture of a compound according to claim 9 where said compound is 2-amino-N-[1-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

11. The compound according to claim 10 where the compound is 2-amino-N-[1-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

12. Th compound according to claim 10 wh re the compound is 2-amino-N-[1-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

13. A compound according to claim 8 wherein R^1 is $-CH_2$-phenyl or $-CH_2$-4-fluoro-phenyl and R^3 is 3-indolyl-CH_2-.

14. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

15. The compound according to claim 14 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

16. The compound according to claim 14 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

17. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

18. The compound according to claim 17 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

19. The compound according to claim 17 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

20. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

21. The compound according to claim 20 where the compound is 2-amino-N-[2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

22. Th compound according to claim 20 where the compound is 2-amino-N-[2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

23. A compound according to claim 8 wherein R^1 is $-CH_2$-phenyl or $-CH_2$-4-fluoro-phenyl and R^3 is phenyl-CH_2-O-CH_2-.

24. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

25. The compound according to claim 24 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

26. The compound according to claim 25 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartaric acid salt.

27. The compound according to claim 24 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

28. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

29. The compound according to claim 28 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

30. The compound according to claim 28 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

31. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-[3a-(R,S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

32. The compound according to claim 31 where the compound is 2-amino-N-{2-[3a-(R)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-isobutyramide.

33. The compound according to claim 31 where the compound is 2-amino-N-{2-[3a-(S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-isobutyramide.

34. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

35. The compound according to claim 34 where the compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

36. The compound according to claim 34 where the compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

37. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

38. The compound according to claim 37 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

39. The compound according to claim 37 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

40. A compound according to claim 5 wherein e is 1; n is 1; w is 1; R^1 is $-(CH_2)_t-A^1$;

where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

t is 0, 1 or 2;

and R^3 is ph nyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or 3-indolyl-CH_2-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

41. A compound according to claim 40 wherein X^5 and X^{5a} are each methyl; R^1 is -CH_2-phenyl, -CH_2-4-fluoro-phenyl, -CH_2-pyridyl or -CH_2-thiazolyl and R^2 is hydrogen, methyl, ethyl, t-butyl or -CH_2CF_3.

42. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

43. A compound according to claim 42 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

44. A compound according to claim 42 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

45. A method for increasing levels of endogenous growth hormone in a human or other animal which comprises administering to such human or animal an effective amount of a compound of claim 1.

46. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an inert carrier and an effective amount of a compound of claim 1.

47. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an inert carrier, an effective amount of a compound of claim 1 and a growth hormone secretagogue selected from the group consisting of GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 and B-HT920 or an analog thereof.

48. A method for treating or preventing osteoporosis which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in treating or preventing osteoporosis.

49. A method for treating or preventing diseases or conditions which may be treated or prevented by growth hormone which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

50. A method according to claim 49 wherein the disease or condition is congestive heart failure, frailty associated with aging or obesity.

51. A method for accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery, which method comprises administering to a mammal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

52. A method for improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis, which method comprises administering to a human or other animal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

53. A method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of a bisphosphonate compound and a compound of claim 1.

54. A method for the treatment of osteoporosis according to claim 53 wherein the bisphosphonate compound is alendronate.

55. A method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of estrogen or Premarin® and a compound of claim 1 and optionally progesterone.

56. A compound according to claim 2 wherein b is 0; X^5 and X^{5a} are each independently hydrogen, $(C_1$-$C_3)$alkyl or hydroxy$(C_1$-$C_3)$alkyl;

R^3 is selected from the group consisting of 1-indolyl-CH_2-, 2-indolyl-CH_2-, 3-indolyl-CH_2-, 1-naphthyl-CH_2-, 2-naphthyl-CH_2-, 1-benzimidazolyl-CH_2-, 2-benzimidazolyl-CH_2-, phenyl-$(C_1$-$C_4)$alkyl-, 2-pyridyl-$(C_1$-$C_4)$alkyl-, 3-pyridyl-$(C_1$-$C_4)$alkyl-, 4-pyridyl-$(C_1$-$C_4)$alkyl-, phenyl-CH_2-S-CH_2-, thienyl-$(C_1$-$C_4)$alkyl-, phenyl-$(C_0$-$C_3)$alkyl-O-CH_2-,

ph nyl-CH_2-O-ph nyl-CH_2-, 3-benzothienyl-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2-, pyridyl-CH_2-O-CH_2-, pyrimidyl-CH_2-O-CH_2- and phenyl-O-CH_2-CH_2;

where the aryl portion(s) of the groups defined for R^3 are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH_3, OCH_3, OCF_3, OCF_2H and CF_3.

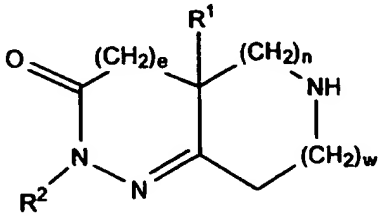
57. A method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of calcitonin and a compound of claim 1.

58. A method to increase IGF-1 levels in a human or other animal deficient in IGF-1 which comprises administering to a human or other animal with IGF-1 deficiency a compound of claim 1.

59. A method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or antagonist and a compound of claim 1.

60. A method according to claim 59 wherein the estrogen agonist or antagonist is tamoxifen, droloxifene, raloxifene or idoxifene.

61. A compound of the formula



(II)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts thereof, wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$,

$-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, -C≡C-, $-N(X^6)C(O)-$, $-C(O)NX^6-$, -C(O)O-, $-OC(O)N(X^6)-$ or -OC(O)-;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with 1 to 3 fluoro, 1 or 2 (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, or 1H-tetrazol-5-yl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted by hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$,

$-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, ph noxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted by one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, or optionally substituted (C_3-C_7)cycloalkyl, where the optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^3 for each occurrence is independently hydrogen or (C_1-C_6)alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6)alkyl, (C_2-C_6)halogenated alkyl, optionally substituted (C_3-C_7)cycloalkyl, or (C_3-C_7)-halogenatedcycloalkyl, where optionally substituted (C_1-C_6)alkyl and optionally substituted (C_3-C_7)cycloalkyl in the definition of X^6 is optionally independently substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 (C_1-C_4)alkyl; or

where there are two X^6 groups on one atom and both X^6 are (C_1-C_6)alkyl, the two (C_1-C_6)alkyl groups may be optionally joined and, together with the atom to which the

two X^6 groups are attach d, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or (C_1-C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^2 is hydrogen then R^1 is not -CH=CH-phenyl.

62. A compound according to claim 61 wherein

w is 0 or 1;

n is 1;

R^1 is hydrogen, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_t-A^1$ or (C_1-C_{10})alkyl where the (C_1-C_{10})alkyl and (C_3-C_7)cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, methoxy, CF_3, OCF_3 and OCF_2H;

R^2 is hydrogen, (C_1-C_8)alkyl, (C_0-C_3)alkyl-(C_3-C_7)cycloalkyl, phenyl, or (C_1-C_3)alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3, OH and methoxy.

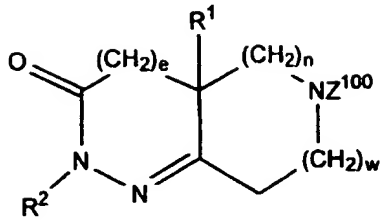
63. A compound according to claim 62 wherein w is 1; e is 0; R^1 is $-CH_2$-pyridyl, $-CH_2$-thiazolyl, or $-CH_2$-phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, (C_1-C_4)alkyl or phenyl where the (C_1-C_4)alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

64. A compound according to claim 63 wherein R^1 is $-CH_2$-phenyl and R^2 is methyl or hydrogen.

65. A compound according to claim 64 wherein the compound is the 3a-(R) enantiomer.

66. A compound according to claim 64 wherein the compound is the 3a-(S) enantiomer.

67. A compound of the formula



(III)

the racemic-diastereomeric mixtures and optical isomers of said compounds, wherein

Z^{100} is methyl, BOC, CBZ, $CF_3C(O)$-, FMOC, TROC, trityl, tosyl, $CH_3C(O)$- or optionally substituted benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, -C≡C-, $-N(X^6)C(O)$, $-C(O)NX^6$, -C(O)O, $-OC(O)N(X^6)$ or -OC(O);

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl,

$-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1; where the alkyl groups and the cycloalkyl groups in the d finition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6)alkyl;

the optionally substituted (C_1-C_6)alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6)alkoxycarbonyl, $-S(O)_m(C_1-C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10})alkanoyloxy or 1 to 3 (C_1-C_6)alkoxy;

X^{12} is hydrogen, (C_1-C_6)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally

substitut d with one to thre substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, or optionally substituted $(C_3$-$C_7)$cycloalkyl, where the optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^3 for each occurrence is independently hydrogen or $(C_1$-$C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, or $(C_3$-$C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted with hydroxyl, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1$-$C_6)$alkyl, $-CO_2(C_1$-$C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 $(C_1$-$C_4)$alkyl; or

where there are two X^6 groups on one atom and both X^6 are $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12};

when R^2 is hydrogen then R^1 is not -CH=CH-phenyl;

when R^2 is H and R^1 is $-CH_2$-CH=CH-Ph, then Z^{100} is not BOC;

when R^2 is H and R^1 is then Z^{100} is not BOC;

when R^2 is H and R^1 is $-CH_2-C(CH_3)=CH_2$, then Z^{100} is not BOC; and

when R^2 is phenyl and R^1 is $-CH_3$, then Z^{100} is not $CH_3C(O)$-.

68. A compound according to claim 67 wherein

w is 0 or 1;

n is 1;

Z^{100} is BOC, methyl, benzyl or CBZ;

R^1 is hydrogen, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_t-A^1$ or (C_1-C_{10})alkyl wh re the (C_1-C_{10})alkyl and (C_3-C_7)cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_7)cycloalkyl, phenyl, or $-(C_1-C_3)$alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3, OH and OMe.

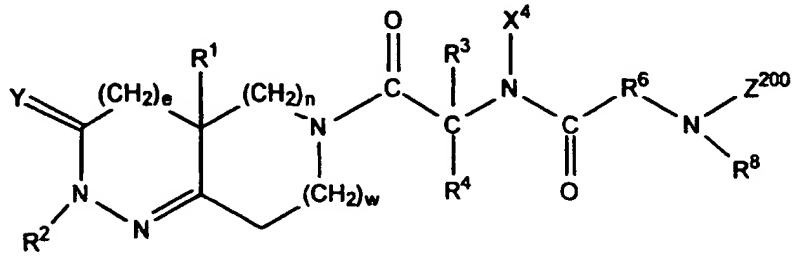
69. A compound according to claim 68 wherein Z^{100} is BOC; w is 1; e is 0; R^1 is $-CH_2$-pyridyl, $-CH_2$-thiazolyl, or $-CH_2$-phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, (C_1-C_4)alkyl or phenyl where the (C_1-C_4)alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

70. A compound according to claim 69 wherein R^1 is $-CH_2$-phenyl and R^2 is methyl or hydrogen.

71. A compound according to claim 70 wherein the compound is the 3a-(R) enantiomer.

72. A compound according to claim 70 wherein the compound is the 3a-(S) enantiomer.

73. A compound of the formula



(IV)

the racemic-diastereomeric mixtures and optical isomers of said compounds, wherein

Z^{200} is t-BOC, CBZ, $CF_3C(O)$-, FMOC, TROC, trityl, tosyl or optionally substituted benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})$alkyl, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)$cycloalkyl, $-(CH_2)_q-Y^1-(C_1-C_6)$alkyl, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)$cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with (C_1-C_4)alkyl, hydroxyl, (C_1-C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6$, -CH=CH-, -C≡C-, $-N(X^6)C(O)$, $-C(O)NX^6$, -C(O)O, $-OC(O)N(X^6)$ or -OC(O);

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4)alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$alkyl, $-CO_2(C_1-C_4)$alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C_1-C_4)alkyl;

R^2 is hydrogen, (C_1-C_8)alkyl, $-(C_0-C_3)$alkyl-(C_3-C_8)cycloalkyl, $-(C_1-C_4)$alkyl-A^1 or A^1;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3, CN or 1 to 3 halogen;

R^3 is A^1, (C_1-C_{10})alkyl, $-(C_1-C_6)$alkyl-A^1, $-(C_1-C_6)$alkyl-(C_3-C_7)cycloalkyl, $-(C_1-C_5)$alkyl-X^1-(C_1-C_5)alkyl, $-(C_1-C_5)$alkyl-X^1-(C_0-C_5)alkyl-A^1 or

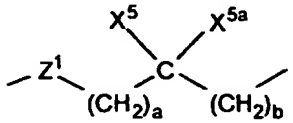
$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl$;

where the alkyl groups in the definition of R^3 is optionally substituted with $-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, $(C_1-C_6)alkyl$ or $(C_3-C_7)cycloalkyl$, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form $(C_5-C_7)cycloalkyl$, $(C_5-C_7)cycloalkenyl$, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or $(C_1-C_6)alkyl$ or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is  ;

where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted $(C_1-C_6)alkyl$;

the optionally substituted $(C_1-C_6)alkyl$ in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1, $-OX^2$, $-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^2$, $(C_3-C_7)cycloalkyl$, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 and X^{5a} forms an alkylene bridge with the nitrogen atom bearing Z^{200} and R^8 where the alkylene bridge contains 1 to 5 carbon atoms provided that X^5 or X^{5a} but not both may be on the carbon atom and Z^{200} or R^8 but not both may be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered

ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or N-X^2, provided that when a and b are both 0 then Z^1 is not N-X^2 or O;

R^8 is hydrogen or optionally substituted (C_1-C_6)alkyl;

where the optionally substituted (C_1-C_6)alkyl in the definition of R^8 is optionally independently substituted with A^1, -C(O)O-(C_1-C_6)alkyl, -S(O)$_m$(C_1-C_6)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C_1-C_{10})alkyl or 1 to 3 (C_1-C_6)alkoxy; or

A^1 for each occurrence is independently (C_5-C_7)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3, OCF_2H, CF_3, CH_3, OCH_3, -OX^6, -C(O)N(X^6)(X^6), -C(O)OX^6, oxo, (C_1-C_6)alkyl, nitro, cyano, benzyl, -S(O)$_m$(C_1-C_6)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X^6)(X^6), -N(X^6)C(O)(X^6), -SO_2N(X^6)(X^6),

$-N(X^6)SO_2$-phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(C_1$-$C_6)$alkyl;

the optionally substituted $(C_1$-$C_6)$alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(C_1$-$C_6)$alkoxycarbonyl, $-S(O)_m(C_1$-$C_6)$alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $(C_1$-$C_{10})$alkanoyloxy or 1 to 3 $(C_1$-$C_6)$alkoxy;

X^{12} is hydrogen, $(C_1$-$C_6)$alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3, OCH_3, OCF_3 and CF_3;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r$-L^1-$(CH_2)_r$-;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, or optionally substituted $(C_3$-$C_7)$cycloalkyl, where the optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1$-$C_6)$alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 $-OX^3$;

X^3 for each occurrence is independently hydrogen or $(C_1$-$C_6)$alkyl;

X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$halogenated alkyl, optionally substituted $(C_3$-$C_7)$cycloalkyl, or $(C_3$-$C_7)$-halogenatedcycloalkyl, where optionally substituted $(C_1$-$C_6)$alkyl and optionally substituted $(C_3$-$C_7)$cycloalkyl in the definition of X^6 is optionally independently substituted with hydroxyl, $(C_1$-$C_4)$alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1$-$C_6)$alkyl, $-CO_2(C_1$-$C_4)$alkyl, 1H-tetrazol-5-yl or 1 or 2 $(C_1$-$C_4)$alkyl; or

when there are two X^6 groups on one atom and both X^6 are $(C_1$-$C_6)$alkyl, the two $(C_1$-$C_6)$alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7;

X^7 is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted by hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12}; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is 2 or 3.

74. A compound according to claim 73 wherein e is 0; Y is O; R^1 is $-CH_2$-phenyl; R^2 is methyl or hydrogen; n is 1; w is 1; R^3 is $-CH_2-O-CH_2$-phenyl; R^4 is hydrogen; X^4 is hydrogen; R^6 is $-C(CH_3)_2-$; Z^{200} is BOC and R^8 is hydrogen.

75. A compound according to claim 56 wherein

R^4 is hydrogen; a is 0; n is 1; w is 1; e is 0;

X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen;

R^7 and R^8 are each hydrogen;

Y is oxygen;

R^2 is hydrogen, methyl, ethyl, propyl, i-propyl, t-butyl, $-CH_2CF_3$, CF_3 or $-CH_2$-cyclopropyl;

R^1 is CH_2-A^1;

where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; and

R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$-, 3-indolyl-CH_2-, thienyl-CH_2-O-CH_2-, thiazolyl-CH_2-O-CH_2- , pyridyl-CH_2-O-CH_2- , pyrimidyl-CH_2-O-CH_2- or phenyl-O-CH_2-CH_2, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

76. A compound according to claim 75

wherein X^5 and X^{5a} are each methyl;

R^2 is methyl, ethyl, or $-CH_2CF_3$;

A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or thienyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to thre substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OM , CF_3, OCF_3 and OCF_2H.

77. A compound according to claim 75

wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3;

A^1 is 2-pyridyl or 3-pyridyl optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H;

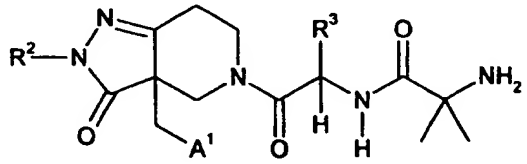
R^3 is phenyl-CH_2-O-CH_2-, phenyl-$(CH_2)_3$- or thienyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

78. A compound according to claim 75

wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3;

A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H; R^3 is 2-pyridyl-CH_2-O-CH_2-, or 3-pyridyl-CH_2-O-CH_2- where the aryl portion is optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3, OCF_3 and OCF_2H.

79. A compound according to claim 77 having the formula



the racemic-diastereomeric mixtures and optical isomers of said compounds wherein

R^2 is methyl; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-3-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-4-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-2,4-di-chloro-phenyl;

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-3-chloro-thiophene; or

R^2 is CH_2CF_3; A^1 is 2-pyridyl; and R^3 is -CH_2-O-CH_2-2,4-di-fluoro-phenyl.

80. Th diast reomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

81. The compound according to claim 80 where the compound is 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

82. The compound according to claim 80 where the compound is 2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

83. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

84. The compound according to claim 83 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

85. The compound according to claim 83 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

86. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

87. The compound according to claim 86 where the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-yl methyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

88. The compound according to claim 86 wh re the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxym thyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-yl methyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

89. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

90. The compound according to claim 89 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

91. The compound according to claim 89 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

92. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

93. The compound according to claim 92 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

94. The compound according to claim 92 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

95. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.